OBSERVATIONS ON THE CAUSAL ORGANISM OF RAT-BITE FEVER IN MAN

BY

ANDREW ROBERTSON, M.B., Ch.B.

(GROCERS' RESEARCH SCHOLAR AND ASSISTANT IN THE DEPARTMENT OF PROTOZOOLOGY, LONDON SCHOOL OF TROPICAL MEDICINE.)

(*Received for publication* 8 *April*, 1924)

In June, 1923, a patient was admitted to the Hospital for Tropical Diseases giving a typical history of rat-bite fever, and showing all the clinical signs of the disease. The clinical aspects of the case have already been published in detail by Dr. G. C. Low (1924), Senior Physician, Hospital for Tropical Diseases, and the following observations have been made on a strain of the parasite derived—thanks to the courtesy of Dr. Low—from this patient.

On 11th June, 1923, two rats and two mice were inoculated with citrated blood from the patient, who was then at the height of a pyrexial attack, the former being given about 3 c.c. each, and the latter 1·5 c.c. all intraperitoneally. Of the four animals inoculated, only one mouse showed the parasite in its peripheral blood. These animals had been bred in the laboratory, and examinations of their blood for several days previous to the inoculation failed to reveal parasites. The appearances and behaviour of the parasite in this mouse were such as to indicate that the organism differed in many respects from the members of the genera *Spirochaeta*, *Leptospira*, etc. to which it has at times been referred, and accordingly search was made through the literature for previous descriptions.

HISTORICAL

Vandyke Carter (1887) published a description of a *Spirillum*, which he discovered in the blood of a rat (*Mus decumanus*), in India. His attention was first drawn to the possible presence of some parasite by a quick, twirling movement of the red blood corpuscles in fresh blood, and, on further investigation, he found that this was due to an organism, which he described as an

'extended and uniformly slender filament of clearly spiral construction, having a length commonly somewhat less than the diameter of a blood disc, but varying from 5 μ to 9 μ . . . . and according to its length presenting from four to eight close spiral turns.'

He was unable to make out the presence of flagella at the ends. The movement of the organism was very active, and consisted of

'rotation round the long axis, propulsion either forward or backward, and occasionally an energetic twisting or lashing.'

From its morphology, movements, and behaviour to reagents Carter concluded that the organism in question was

'a bacterium belonging to the genus spirochaete . . . . such as from its small dimensions might be named provisionally *Spirillum minor*.'

Attempts to inoculate the organism into another rat and also into a monkey were not successful.

There seems to be little doubt that the organism, which Carter found in the blood of the rat, is the same as that which causes rat-bite fever in man.

Thereafter there occur numerous mentions of similar organisms, which were found in the blood of animals. Lingard (1899) found a small *Spirillum* in the blood of a bandicoot (*Mus giganteus*). This he was able to inoculate into rabbits and guinea-pigs, but in the latter it was possible to demonstrate the organism only in the final stages of the infection. While Lingard's description of the parasite is lacking in detail, its behaviour in inoculated animals is similar to that of the virus of rat-bite fever as reported by various workers.

Borrel (1905) found a spirochaete in cancer growths of mice. This work was confirmed by Calkins and Clowes (1905), Deetjen (1906) Tyzzer (1906-07), and Gaylord (1907). There is a marked similarity between the organisms described by these workers, although the measurements varied considerably.

Wenyon (1906) described a spirochaete in the blood of mice which he named *Spirochaeta muris*. This he considered to be identical with the spirochaete found by Borrel, but with reference to the organism of Carter he states that

'since the morphological characters of spirochaetes are not sufficient to establish the identity of any form it is necessary to rely on other characters, notably their behaviour in various hosts, and their pathogenic or other action. As nothing is known of Carter's *Spirillum* of the rat apart from its morphology, the spirochaete of the mouse must be considered to be new to science.'

Morphologically, Wenyon's *Spirochaeta muris* closely resembled Carter's *Spirillum*, and the characteristic movements were also present. Wenyon was unable to demonstrate flagella, but suspected that they might be present, since all the movements of the organism seemed to indicate their presence. The spirochaete was easily inoculable into mice, but could not be demonstrated in guinea-pigs.

Breinl and Kinghorn (1906) isolated a spirochaete from the same source as Wenyon, viz.:—a mouse inoculated with *Trypanosoma dimorphon*, which was sent to them from Paris. They also found a similar spirochaete in the blood of a wild mouse. The parasite was smaller in size than that described by Carter, and accordingly, since they considered it to be a distinct organism, they named it *Spirochaeta laverani*.

MacNeal (1907) demonstrated the presence of flagella at the ends of the spiral in a strain of the parasite isolated from one out of thirty-nine rats (*Mus decumanus*), caught at Morgantown. He considered this organism to be identical with those of Carter, Wenyon, Breinl and Kinghorn, and Nicolle and Compte (in a bat). Despite the fact that he thought his organism to be the same as that of Carter, and that terminal flagella had been seen, MacNeal adopted Wenyon's name *Spirochaeta muris* (var. *Virginiana*).

In man, rat-bite fever has long been recognised as a definite clinical entity. Early accounts of the disease were given by Wilcox (1840) in America, Millot-Carpentier (1884) in France, Peña y Maya (1885) in Spain, Miyake (1889) in Japan, and Horder (1909) in England. While it was soon recognised that the disease depended on the introduction of some virus into the wound caused by the bite of the rat, nevertheless it was comparatively recently that it was associated with a definite organism. That more than one disease may be inoculated into man by the bite of a rat is practically certain, and this led to some confusion, in that some of these diseases were mistaken for the fever of the relapsing type, which is the clinical entity known as rat-bite fever. Shikami (1907) attributed rat-bite fever to a member of the Telosporidia ; Middleton (1910) thought that the causative organism was a *Diplococcus ;*

Ogata (1911), who produced rat-bite fever experimentally by allowing a rat to bite guinea-pigs, considered that the disease was due to an *Aspergillus;* Proescher (1911) described *Bacilli,* which were very numerous in the base of the wound; Schottmüller (1914), Blake (1916) and Tileston (1916) isolated from the blood of patients, who had been bitten by rats and by a South African squirrel, a *Streptothrix,* which was named *Streptothrix muris ratti.* With reference to this last, it is of interest that Tunnicliff (1916) isolated a similar *Streptothrix* from rats with broncho-pneumonia. Hata (1912), Surveyor (1913) and Dalal (1914) reported cures by the use of salvarsan, arguing that, on account of the periodicity of the fever and the peculiar eruption, the infecting organism might be allied to the *Spirochaetae.*

It was, however, left to Futaki (1915) and his co-workers to discover the causative organism of rat-bite fever in man. This was a spiral organism having flagella at the ends, varying in length from 2μ to 5μ, and when the flagella are included from 6μ to 10μ. They named it *Spirochaeta morsus muris,* and considered it to be of the nature of a *Treponema.* The movements of *S. morsus muris* were very rapid, 'resembling those of a vibrio.' It stained readily with Giemsa's stain. Animal experiments were successful; monkeys, mice, house rats and white rats were inoculated with positive results. These authors also claim to have cultivated the parasite on Shimamine's medium, but the culture organisms, as described and figured, differed very considerably from the forms found in man and animals. In cultures, forms appeared up to 19μ in length, and having at times as many as nineteen coils. The coils or spirals were wider than those of the blood forms—one coil to 2μ, whereas the blood forms had one coil to 1μ. Whether it was possible successfully to inoculate these cultural forms into experimental animals is not stated. Further mention of these cultural forms will be made later.

Futaki and his associates were of the opinion that the organism, which they had isolated, differed in certain respects from those previously described as occurring in the blood of mice, rats and other animals, and further, that, as no connection between these organisms and rat-bite fever in man had been demonstrated, they were justified in considering that the parasite was a new species.

Ishiwara, Ohtawara and Tamura (1915) dealt with certain experimental aspects of the question. They allowed infected rats to bite guinea-pigs, thus confirming the work of Ogata, and studied the course of the disease in these animals. They discussed the similarity of Wenyon's *Spirochaeta muris* and the *Spirochaeta laverani* of Breinl and Kinghorn to *S. morsus muris*. Ishiwara and his associates did not succeed in cultivating it.

Kaneko and Okuda (1917), dealing with the organism in man, came to the conclusion that the long and short forms described by Futaki were not diverse in type. The short forms were found in the peripheral blood, but the long forms—similar to the cultural forms of Futaki—they found in renal casts, in the tissues of the kidneys and in the suprarenals. This change in the morphology they attribute to the formation of immune bodies in the patient, and are of the opinion that the long forms are really old and degenerate individuals.

Ido, Ito, Wani and Okuda (1917) obtained blood serum from three human patients recovering from rat-bite fever. The effect of this serum they tested on spirochaetes in the blood of guinea-pigs, which had been infected from a wild rat, *Mus decumanus*, and found that the organisms were killed, whereas in controls treated with serum from patients who had not had rat-bite fever, and also with isotonic salt solution, the spirochaetes remained actively motile and relatively numerous. This is of interest in that, in addition to illustrating the action of immune serum on the parasites, it suggests a certain degree of association between the causative organism of rat-bite fever in man, and similar parasites found in the peripheral blood of mice and rats.

Row (1917) isolated a spiral organism from a case of human rat-bite fever in India. This was rather smaller in size than that described by the Japanese workers, 3μ to 5μ in length, and Row thought it a distinct species. Later, in 1922, Row named his organism *Spirochaeta petit*. Row found that

> 'the broad distinction made by Futaki into the long and short forms according to the situation from which the virus is derived—the long forms from lymphatic nodules and short ones from the peripheral blood—does not hold good in Bombay.'

The Bombay virus was not fatally virulent to guinea-pigs and rats. Row came to the conclusion that the number of spirochaetes in the organs of infected animals was not greater than could be accounted for by the blood supply to these organs, and that such as were found were uniform in type with those present in the peripheral blood. The Bombay virus was shorter than that described by the Japanese workers, and was more slender than English strains. The fact, too, that at first the flagella of the Bombay strain were not seen, was an additional reason why Row should place his spirochaete in a new species. Parmanand (1923), however, demonstrated the terminal flagella in this strain, and came to the conclusion that it was similar to the *Spirochaeta morsus muris* of Futaki.

Izumi and Kato (1917), by serological methods, proved the relationship of the spirochaete found in cases of cat-bite disease to that of rat-bite fever.

Manson-Bahr (1922), in 'Manson's Tropical Diseases,' referred the causative organism of rat-bite fever to the genus *Leptospira*, and retained the specific name *morsus muris*. His reasons for making this alteration in the nomenclature were not stated. Sangiorgi (1922) suggested the generic name *Treponemella* for the rat-bite virus.

Numerous reports of cases of rat-bite fever have appeared in the literature since the discovery of the parasite by Futaki and his associates, and the foregoing is not intended to be an exhaustive survey of the literature on the subject. As many of those communications, which have a direct bearing on the parasite, its morphology, nomenclature, etc., as possible, have been mentioned, but many other papers on the subject will be found in the list of references.

THE PRESENT CASE

While the patient was having one of his periodical bouts of fever, specimens of his blood, saliva, and urine were examined. In the blood, both in stained preparations and in fresh preparations examined with dark ground illumination, no organisms were found. In the urine, also, the results of the search were negative. The saliva proved to have the usual number of spirochaetes of all kinds, but there was also present an undoubted *Spirillum*, which, however, was so scarce that accurate observations could not be made. At the time of the examination the patient showed the typical, dark purplish-red, exanthematous rash, especially over the lower ribs and upper part of the abdomen on the right side. One of the most conspicuous patches of the rash was chosen, and its surface scarified. Gentle pressure was applied to the scarified area, and preparations of the exuded serum were examined with the dark ground. In one specimen only were the organisms found. Stained films from this source were negative.

A strain of the parasite was isolated in the blood of mice, which had been inoculated with citrated blood from the patient.

MORPHOLOGY

The body of the organism, which is coiled into a more or less perfect spiral, is rigid. Occasionally, under certain circumstances, the body may be bent, but as soon as the factors which cause the bending are removed, it returns to the original state. In comparison with the members of the genus *Spironema* this rigidity is most striking. The *Spironemata*, in addition to the general flexibility of their bodies, progress by means of an undulating movement, which passes from one end of the body to the other ; the rat-bite organism, on the other hand, retains its fixed shape during movement, although in dark ground preparations the rapid spinning of the body may simulate a wave-like mode of progression. At each end of the spiral body are flagella, usually single but sometimes multiple, and their function seems to be not so much to propel the organism, as to produce the spinning movement of the body, which then passes through the fluid much in the same manner as a screw enters wood. Movement, which is very rapid, is usually in more or less of a straight line, but sometimes consists of sudden dashes to and fro, or in any direction, when either end of the body may be, for the time being, the anterior. Lashing movements of the body are also seen, but there is a possibility that this may be due to the artificial conditions under which the observations are made, such as the fixation of the flagellum at one end to the under surface of the cover glass, to a group of red blood corpuscles, etc.

With regard to the size of the parasite considerable variations have been noted. Thus it varies in different animals, and also in the same animal from day to day. There appears to be a certain tendency to uniformity of size in any given animal on any given day, by which is meant that one day the preponderating forms will be, for example, long forms, whereas the following day, or subsequently, the majority observed will be shorter or medium-sized. The largest forms seen were between 14μ and 15μ including the flagella, *i.e.*, slightly more than double the diameter of the red blood corpuscles of the mouse, and, when body length only is considered, the maximum measurements were between 9μ and 10μ. It should be noted that the length of the flagella is by no means proportionate to the dimensions of the body, as small forms with a body-length of only 2·5μ may have flagella as long as individuals with a body-length of 8μ or thereby. The smallest individuals measured 3·25μ, but these had a flagellum at one end only. The smallest body-length was 1·5μ. The average size was between 3μ and 5·5μ, and including the flagella between 6μ and 8μ.

The number of coils or turns of the body varies from one-and-a-half to eight or nine. The width of the body, owing to its spiral construction, is extremely difficult to ascertain with accuracy. Fixed and stained preparations are of little value in this respect, as the degree of distortion is very great. The average width is about 0·2μ, and the width of the spiral as a whole about 0·7μ.

Division takes place by transverse binary fission of the body into two, more or less equal portions. A constriction appears about the middle of the body, and this gradually deepens until the two parts are connected by the merest thread. Certain peculiarities of movement may be seen in these dividing forms owing to the different alignment of the two halves. Finally, the two portions separate, giving rise to two new individuals, which, at first, have flagella at one end only. Later a flagellum appears at the other end. It seems probable that the fully developed organism has a flagellum at each end, and that those forms with flagella at one end only are the products of division. In stained preparations it is quite common to find the flagella at each end to be multiple, but this seems to be more the result of the fixation than a characteristic of the parasite, as, in fresh specimens in which the movement has slowed, it has only rarely been possible to demonstrate more than one flagellum. For some reason, the flagella are very difficult to stain, and even using the same technique, constant results cannot be obtained. Several stains have been tried and various methods of fixation, but the best results have been obtained with slight modifications of Leishman's and Giemsa's stains.

Futaki and his co-workers described two forms of the parasite, the first as found in the peripheral blood, the second longer forms in cultures. Kaneko and Okuda mentioned similar long forms, which they found in the kidneys, suprarenals and renal tube casts, and these they interpreted as older and somewhat degenerate individuals. Morphologically, there is a great difference between the cultural forms and the blood forms, the former being as many as 19μ in length and having coils twice as wide as the blood forms, and indeed this variation, especially in view of the fact that no one has succeeded in cultivating the rat-bite virus since Futaki, is so marked that it is necessary to bear in mind the possibility that in the infected animals and cultures, there were spirochaetes other than that of rat-bite fever. In the present case careful search was made in the tissues of animals which were killed during their convalescence from the disease, and also at various stages in the course of the infection, with the result that no true spiral organisms were found other than the forms described above as occurring in the peripheral blood. Hogue (1924), working on *S. eurygyrata*, has shown that the cultural forms of a spirochaete may differ markedly in their morphology from the forms found under natural conditions, but even this is insufficient to explain the difference in length, shape, structure, etc., between the blood forms and Futaki's cultural forms. It is significant, also, that it was not possible to inoculate successfully experimental animals with the cultures.

CULTIVATION EXPERIMENTS

In the present case all attempts to cultivate the virus have so far proved unsuccessful. N.N.N. (Novy, MacNeal, Nicolle), Noguchi's and Shimamine's media and a dilute blood agar were the chief media used. These were incubated at different temperatures but without result. The cultural experiments are being continued.

ANIMAL EXPERIMENTS

Of four animals inoculated from the patient, only one mouse showed the parasite in its peripheral blood on the seventh day after inoculation. The other mouse and the two rats never showed parasites. Mice proved to be most convenient animals in which to carry on the infection, because the *Spirilla* appeared in such relatively large numbers in their blood, and also because they seemed to be little incommoded by the disease. The average length of time which elapsed after inoculation and before parasites appeared was five days, and the infection reached its maximum intensity, so far at least as numbers were concerned, on the ninth day after inoculation. It was quite common, however, for the parasites to show up in fair numbers about the fifth day, disappear the following day, and return in increased numbers on the seventh or eighth day, when they remained constantly present for some weeks. No explanation of this temporary disappearance is known. The shortest period before *Spirilla* could be detected was three days, and the longest fourteen days. Having so quickly reached its maximum intensity the infection gradually declined, the numbers in the blood becoming less and less, until finally they disappeared entirely. As a rule, it is possible to recover the strain by inoculating the blood of the convalescent mouse, even after the *Spirilla* cannot be demonstrated microscopically owing to their scarcity, into a fresh animal. The infection usually persists for the matter of six weeks or so, but, in this instance at least, considerable trouble has been experienced by the mice dying from intercurrent affections.

Guinea-pigs, when inoculated with this strain, showed symptoms of disease. A few days after inoculation, usually about two-and-a-half to three days, there was a definite rise in temperature, which was followed at irregular intervals by similar febrile attacks. During this period, which usually lasted between twenty-one and twenty-four days, the animals were definitely ill, as shown by loss of appetite, poor condition of the fur, general weakness, etc. At the end of this time the disease seemed to reach its most crucial point, and the guinea-pigs were very ill indeed, but this was followed by a gradual convalescence, and in no instance did the animals die from the infection.

It was not possible to demonstrate the *Spirilla* in the blood of the guinea-pigs at any stage, nor were mice successfully inoculated with their blood. These findings are of interest in comparison with those of other workers. Certain strains have proved to be lethal to guinea-pigs, whereas others have caused them little inconvenience ;

some strains have shown parasites in the peripheral blood over a comparatively long period, while others have only appeared immediately before the death of the animal or not at all. One of the guinea-pigs was inoculated subcutaneously in the leg, and this was followed by a painless, oedematous swelling, which persisted until the twenty-first day after. This animal also showed symptoms of the generalised disease.

After the guinea-pigs had recovered, it was found that their serum, when mixed in equal quantities with the blood of mice containing *Spirilla*, rendered the parasites immobile in twenty minutes, whereas in control experiments, the blood of the mice being mixed with serum from uninfected guinea-pigs, with serum from guinea-pigs with various strains of trypanosomes, and with normal saline, the organisms were as actively motile after two hours as they appeared to be when the blood was freshly drawn. The immune bodies in the serum do not seem to be very powerful, since, in dilutions less than about one in four, their effect on the *Spirilla* was very slight. So far no signs of agglutination of the parasites have been seen, although this phenomenon has been described. Mouse blood containing *Spirilla* was mixed with equal parts of immune guinea-pig serum and allowed to stand for fifteen minutes, and was then inoculated into a fresh mouse. Mice, which were inoculated at the same time with untreated blood, showed a heavy infection in five days, whereas this one did not show infection till a considerable time after, and even then the parasites were so few in number that it was only by careful search that they could be demonstrated.

Of the two rats which were inoculated with the blood from the human patient, one died in a few days, while the other never showed parasites in its blood or any signs of disease. It has been possible to find parasites in scanty numbers in the blood of young inoculated rats, but, unless the rats were very young indeed, the *Spirilla* never became evident.

DISCUSSION

It has been suggested by several workers that the rat-bite fever organism is more closely allied to the genus *Spirillum* than to the *Spirochaeta*, and that is the opinion arrived at by the study of the present strain.

Dobell (1918) discussed the nomenclature of the spirochaete of syphilis. He pointed out that this parasite was morphologically so different from the type species of the genus *Spirochaeta*, viz. :—*S. plicatilis*, that it could not be placed in the same genus. The rat-bite fever organism, with its non-flexible body, terminal flagella and absence of an axial filament, is even more divergent in character, and accordingly cannot be referred to the genus *Spirochaeta*.

For practically the same reasons the rat-bite organism cannot be placed in the genus *Spironema*, the type species of which is *S. pallidum* (Schaudinn, 1905) Vuillemin, 1905.

Manson-Bahr (1918) named the rat-bite fever parasite *Leptospira morsus muris*. He did not state his reasons for thus altering the generic name, but it seems probable that he was influenced, firstly, by the cultural forms of Futaki, which, as figured, have some resemblance to *Leptospira*, and, secondly, by the forms described by Kaneko and Okuda in tissues, renal casts, etc. Now it has been shown by Hogue (1922), working on *S. eurygyrata*, that the cultural forms of a spirochaete may differ from the forms found in nature to a considerable degree, but the dissimilarity of the blood forms and Futaki's cultural forms is too marked to be explained on this basis. With regard to the forms found in tissues, careful search has been made in the organs of animals infected with the present strain, which have been killed at various stages of the infection and also during convalescence, without finding any spiral organism other than the form as described in the peripheral blood. This is in agreement with the findings of Row and other workers. In the present case, in attempting to cultivate the parasite on Shimamine's medium, numerous filaments were found, which closely simulated the appearances of *Leptospira* and of *Spironemata*. It therefore seems probable that Kaneko and Okuda have been dealing with some spirochaetal infection superimposed on that of the rat-bite fever organism, and that Futaki and his co-workers have either cultivated some other organism, or have mistaken the filamentous threads in the medium for true spirochaetes. The work of Thomson (1923) on pseudo-spirochaetes may have some bearing on this question.

The conclusion must be arrived at that the rat-bite fever organism with its terminal flagella, and non-flexible, non-undulating, spiral body should be referred at present to the genus *Spirillum*, Ehrenberg, 1830.

In the consideration of the specific name, which should be applied to the rat-bite fever organism, the first point to be decided is whether more than one distinct species of *Spirillum* has been described in the blood of mice and rats, bandicoots, etc., and if not, whether this is the same as that causing rat-bite fever. Firstly, as regards the *Spirilla* in the blood of mice, rats, etc., the prior discovery of such an organism rests with Carter. That Carter was dealing with a true *Spirillum* seems clear from his description of the morphology and of the characteristic movements. Following Carter, the *Spirochaeta muris* of Wenyon, with which can be grouped the *Spirochaeta laverani* of Breinl and Kinghorn as it came from the same source, was the next to be given a specific name. That this was a *Spirillum* also there is now no doubt, and so far as its morphology is concerned, its variations from *Spirillum minor* are such as may be seen in different strains of the same species. Carter was unable to demonstrate his organism in an experimentally infected rat and monkey, but this is quite in accordance with the findings of later workers using strains of the rat-bite parasite. It is quite impossible to prove that Wenyon, and the large number of workers such as Lingard, Borrel, Deetjen, etc., who found similar spiral organisms in mice and other animals, but did not name them, were not dealing with distinct species, but the contention is that the bulk of evidence, in view of more recent work, is so strongly suggestive as almost to amount to a certainty that they were describing *Spirillum minor.* Admittedly slight differences do occur, in morphology and also in the action on inoculated animals, but similar differences are found in undoubted rat-bite fever strains, and it is suggested that these variations are insufficient to justify the bestowal of new generic and specific names.

The question next arises as to whether the organism isolated by Futaki and his associates is the same as those described in the blood of mice, etc., by the previous workers. In parenthesis it may be said that the *Spirochaeta petit* of Row, in view of the work of Parmanand, is here considered to be the same as the *S. morsus muris* of the Japanese workers, and that, therefore, only one species of *Spirillum* is known to cause true rat-bite fever in man.

The problem resolves itself to this : does there exist in the blood of mice, rats, cats, etc., a *Spirillum* which can be distinguished from other *Spirilla* in the same animals, only by its transmissability to man ? This, needless to say, is incapable of absolute proof either way, but the submission is that the preponderance of evidence points to the non-existence of a distinct ' human ' species.

1. As regards morphology the forms isolated in human strains cannot be differentiated from the forms in animals naturally infected.

2. Human strains differ from each other in their inoculability into, and reaction in experimental animals. Thus one strain may be highly virulent in guinea-pigs, and show parasites in the animals' blood, whereas another may cause some temporary discomfort only. One strain may be easily inoculable into rats and another may not. Such differences as do occur between human and animal strains in their inoculability and reactions are no greater than may be found in two divergent human strains.

3. It has been proved that serum from patients recovering from rat-bite fever, and also cat-bite disease, contains immune bodies which will immobilise *Spirilla* isolated from naturally infected wild rats.

The conclusion arrived at is that the *Spirillum*, which causes rat-bite fever in man, is the same as the one which occurs naturally in the blood of animals. Following the rule of priority, therefore, the name for the causal organism should be *Spirillum minor*, Carter, 1887. Unfortunately, in naming his organism, Carter did not take into account the fact that the generic name *Spirillum* is neuter. When such a mistake in gender has been made, it is permissible, under the International Rules of Botanical Nomenclature (Art. 57), to make the necessary correction, while the corrected name is cited from the original author and publication. *Spirillum minor*, therefore, becomes *Spirillum minus*, Carter, 1887.

CONCLUSION

1. Up to the present there is no reason for supposing that the *Spirilla* in the blood of naturally infected mice, rats, bandicoots, etc., belong to more than one species.

2. The species of *Spirillum*, which is the causal organism of rat-bite fever in man, is not distinct from the species found naturally in the blood of animals.

3. The correct name for the causal organism of rat-bite fever in man is

Spirillum minus, Carter, 1887.

Synonyms :

Spirochaeta laverani, Breinl and Kinghorn, 1906.
Spirochaeta muris, Wenyon, 1906.
Spirochaeta morsus muris, Futaki, Takaki, Taniguchi and Osumi, 1917.
Leptospira morsus muris (Futaki, Takaki, Taniguchi and Osumi, 1917) emend. Manson-Bahr, 1922.
Spirochaeta petit, Row, 1922.
Treponemella muris (Wenyon, 1906), emend. Sangiorgi, 1922.
Spironema minor (Carter, 1887), emend. Sangiorgi, 1922.

REFERENCES

Atkinson, A. G. (1912-13). Rat Bite Fever. *Med. Chron.*, Manchester, Vol. LVII, p. 1.

——— (1913). Rat Bite Fever. *Med. Chronicle*, Vol. XXV, p. 1.

Bais, W. J. (1917). Rattenbeetsiekte. *Geneesk. Tijdschr. v. Nederl.-Indië*, Vol. LVII, No. 3, p. 357.

Balfour, A. (1906). A Haemogregarine of Mammals and Some Notes on Trypanosomiasis in the Anglo-Egyptian Soudan. *Jl. Trop. Med. & Hyg.*, Vol. IX, p. 90.

Blake, F. G. (1916). The Etiology of Rat Bite Fever . *Jour. of Exper. Med.*, Baltimore, Vol. XXIII, No. 1, p. 39.

Borrel, M. A. (1905). Infection vermineuse et Spirochètes chez les Souris cancéreuses. *Compt. Rend. Soc. Biol.*, Vol. LVII, p. 770.

Borelli, E. (1918). Le iniezioni mercuriale nella cura del Sodoku. *Policlinico*, Vol. XXV, No. 2, p. 25.

Breinl, A., and Kinghorn, A. (1906). A Preliminary Note on a New *Spirochaeta* found in a Mouse. *Lancet*, Vol. ii, p. 651.

Calkins, G. N., and Clowes, J. H. A. (1905). Some Artefacts in Mouse Carcinoma. *Jour. Infect. Dis.*, Vol. II, p. 555.

Carter, H. V. (1887). Note on the Occurrence of a Minute Blood Spirillum in an Indian Rat. *Sci. Mem. by Med. Off. of the Army of India*, Part 3, p. 45.

Cavina, G. (1917). Un cas di Sodoku in un soldata. *Morgagni*, Part I, Archivo, Vol. LIX, No. 8, p. 258.

Cazamain, P. (1921). Fièvre par morsure de chien. *Bull. et Mém. Soc. Méd. Hôpit. de Paris*, 3e Sér., Vol. XLV, No. 7, p. 628.

Chagas, C. (1915). Verificão no Rio de Janeiro da molestia Sodoku (Rattenbisskrankheit) devida a mordedura de rato. *Brazil Med.*, Vol. XXIX, No. 28, p. 217.

Coles, A. C. (1918). Rat-Bite Fever. (Correspondence) *Lancet*, Vol. i, p. 350.

Costa, S., and Troisier, J. (1918). Un nouveau cas de 'Sodoku' (Fièvre par morsure de rat). Spirochètes à l'examen direct du sang. *Bull. et Mém. Soc. Méd. Hôpit. de Paris*, Vol. XLII, No. 21-22, p. 616.

Crohn, B. B. (1915). Rat Bite Fever. *Arch. Intern. Med.*, Vol. XVI, No. 6, p. 1014.

Cruikshank, R. W. (1912). A Note on Rat Bite Fever, with Report and Temperature Chart of a Recent Case. *Brit. Med. Jour.*, Vol. ii, p. 1437.

Curtillet, J., and Lombart, P. (1912). *Journ. de. Méd. int.*, Paris, Vol. XVI, p. 335.

Dalal, A. K. (1914). Case of Rat Bite Fever, treated with Intravenous Injection of Neo-Salvarsan. *The Practitioner*, Vol. XCII, p. 449.

Deetjen, H. (1906). *Münch. med. Woch.*, Vol. XLIII, p. 1167.

Delamare, G., and Mouchet, A. (1923). Examen histologique de la cicatrice cutanée, d'un tronc lymphatique et d'un ganglion dans un cas de sodoku. *Bull. et Mém. Soc. Méd. Hôpit. de Paris*, 3rd Ser., Vol. XXXIX, No. 20, p. 845.

Dick, M. J. and Rutherford, W. J. (1913). A Case of the so-called Rat-Bite Disease. *Brit. Med. Jour.*, Vol. ii, p. 1581.

Douglas, S. R., Colebrook, L., and Fleming, A. (1918). A Case of Rat-Bite Fever. *Lancet*, Vol. i, p. 253.

Ehrenberg, D. C. G. (1830). *Abhandl. der Berliner Akademie*, p. 38. (According to Ehrenberg, 1838).

Farquhar, O. C. (1869). *Cincinnati Lancet and Obs.*, Vol. XII, p. 650.

Fievez, J. (1916). Un cas de Sodoku (Septicémie éruptive par morsure de rat) observé dans la zone des armées. *Paris Méd.*, Vol. VI, No. 16, p. 388.

Foulerton, A. G. R. (1919). The Rat as a Carrier of Disease Transmissible to Man and Other Lower Animals. *Jour. Com. Path. and Therap.*, Vol. XXII, Part 3, p. 182.

——— (1919). The Protozoal Parasites of the Rat, with Special Reference to the Rat as a Natural Reservoir of *Spirochaeta icterohaemorrhagiae*. *Jour. Path. and Bacteriol.*, Vol. XXIII, No. 1, p. 78.

Frugoni, C. (1911). *Riforma med.*, Vol. XXVIII, p. 1298.

——— (1911). Intorno al Primo Caso Diagnosticato in Italia di Sodoku (Rattenbisskrankheit). *Rinista Critica di Clinica Medica.*, Vol. XII, No. 50-51.

——— (1912). Sodoku (Rattenbisskrankheit). *Berliner Klin. Wochenschr.*

Futaki, K., Takaki, J., Taniguchi, T., and Osumi, S. (1916). The Cause of Rat Bite Fever. *Jour. of Exper. Med.*, Baltimore, Vol. XXIII, No. 2, p. 249.

——— ——— ——— ——— (1917). *Spirochaeta morsus muris* n. sp. The Cause of Rat Bite Fever. 2nd Paper. *Journ. of Exper. Med.*, Baltimore, Vol. XXV, No. 1, p. 33.

——— ——— ——— ——— (1917). Rat-Bite Disease. Spirochaetes inoculated into Guinea Pigs. *Iji Shimbun*, No. 985, p. 1513.

——— ——— ——— ——— (1917). Spirochaetes found in Rat Bite Disease and their significance. *Mitteil Med. Gesellsch. z. Tokyo*, Vol. XXXI, No. 22, p. 83.

Gaylord, H. R. (1907). *Ann. Rep. Cancer Lab.*, New York State Dept. Health., Vol. VIII, p. 34.

Gouget, A. (1912). *Presse Méd.*, Vol. XX, p. 186.

Grenet, H., and Lehucher (1918). Quelques cas de Sodoku. *Bull. et Mém. Soc. Méd. Hôpit. de Paris*, 3e Sér., Vol. XXXIV, No. 3-4, p. 73.

Gupta, B. M. (1922). Short Notes on a Case of Rat-Bite Fever in Shillong. *Indian Med. Gaz.*, Vol. IV, p. 139.

d'Halluin, P., and Fievez, J. (1918). Un cas de Sodoku subaigue. *Paris Méd.*, Vol. VIII, No. 12, p. 234.

Hata, S. (1912). Salvarsantherapie der Rattenbisskrankheit in Japan. *Münchener Med. Woch.*, Vol. LIX, No. 16, p. 854.

Hewlett, R. T. and Rodman, G. H. (1913). A Case of Rat-Bite Disease. *The Practitioner*, Vol. XIX, p. 86.

Hogue, M. J. (1922). *Spirochaeta eurygyrata.* A Note on its Life History and Cultivation. *Jour. Exper. Med.*, Vol. XXXVI, No. 6, p. 617.

Horder, T. J. (1909). Rat-Bite Fever. Three Cases. *Quart. Jour. Med.*, Vol. III, p. 121.

Ido, Y., Ito, H., Wani, H., and Okuda, K. (1917). Circulating Immunity Principles in Rat-Bite Fever. *Jour. of Exper. Med.*, Baltimore, Vol. XXVI, No. 3, p. 377.

Ishiwara, K., Ohtawara, T., and Tamura, K. (1916). Rat Bite Disease. Demonstration of the Spirochaetes in Healthy Rats. *Tokyo Igakkwai Zassi*, Vol. XXX, No. 14, p. 52.

——— ——— ——— (1917). Experimental Rat-Bite Fever. First Report. *Jour. of Exper. Med.*, Vol. XXV, No. 1, p. 45.

ISHIWARA, K., OHTAWARA, T., and TAMURA, K. (1917). Spirochaetes in Rats. *Hifukwa Hitsunyokwa Zasshi.* (*Japan. Zeitschr. f. Derm. u. Urol.*), Vol. XVII, No. 2., p. 87.

——— ——— ——— (1917). Über ein neues Symptom der experimentellen Rattenbisskrankheit, die Sklerose and der Impfstelle. *Verhand. Japan. Path. Gesellsch.*, Vol. VII, p. 143.

IZUMI, G., and KATO, M. (1917). Cat-Bite Disease and its Pathogenicity. *Tokyo Iji Shinshi*, No. 2021, p. 1.

KANEKO, R., and OKUDA, K. (1917). A Contribution to the Etiology and Pathology of Rat Bite Fever. *Jour. of Exper. Med.*, Baltimore, Vol. XXVI, No. 3, p. 363.

KASAI, K. (1921). On the Differential Diagnosis of *Spirochaeta morsus muris* and *S. muris. Chuwo Juikwai Zasshi*, Vol. XXXIV, No. 7.

——— (1922). A Comparative Study of Rat Bite Fever Spirochaetes and Rat Spirochaetes. *Saikingaku Zasshi*, No. 324 (Summarised in *Japan Med. World*, Tokyo, 1923., Vol. III, No. 3, p. 54).

KITAGAWA, J. (1917). Clinical Experience with Cat-Bite Disease. *Saikingaku Zasshi*, No. 260, p. 422.

KITAGAWA, J., and MUKOYAMA, T. (1917). The Etiologic Agent of Rat-Bite Disease. Preliminary Report. *Arch. Intern. Med.*, Vol. XX, No. 3, p. 317.

KITAKAWA, T. (1916). Spirochaete found in Cases of Rat-Bite Disease. *Saikin Gaku Zassi*, No. 249, p. 75.

KOBAYASHI, R., and KODAMA, M. (1919). A Contribution to the Study of *Spirochaeta morsus muris* in the Nippon Field Vole (*Microtus montebelle*), *Kitasato Arch. of Exper. Med.*, Vol. III, No. 3, p. 199.

KUNHARDT, J. C. G. (1919). The Rat Problem of India. *Indian Jour. Med. Res.* (Spec. Indian Sci. Congress Number, 1919), p. 145.

KUSAMA, S., KOBAYASHI, R., and KASAI, K. (1919). The Rat-Bite Fever Spirochete, with Comparative Study of Human, Wild Rat, and Field Vole Strains. *Jour. Inject. Dis.*, Vol. XXIV, No. 4, p. 366.

KUSAMA, S., KOBAYASHI, R., and KUZUNSHI, K. (1918). Spirochaete of Rat-Bite Fever. *Saikingaku Zassi*, No. 271, p. 1.

LAGRIFFE, and LOUP (1914). Un Cas de Sodoku. *Presse Méd.*, No. 31, p. 456.

LINGARD (1899). Report on Surra in Equines, Bovines, Buffaloes and Canines, together with an account of experiments conducted with trypanosomes of Rats, Bandicoots, and Fish. Vol. II, Part 1.

LOW, G. C. (1924). A Case of Rat-Bite Fever in England. Recovery of the Spirochaete from the Blood. *Brit. Med. Jour.*, Vol. i, p. 236.

LOW., G C., and COCKIN, R. P. (1918). A Case of Rat-Bite Fever Treated Successfully by Injections of Novarsenobillon. *Brit. Med. Jour.*, Vol. i, p. 203.

LÖWENTHAL, W. (1906). *Berl. Klin. Woch.*, Vol. XLIII, p. 283.

MACNEAL, W. J. (1907). A Spirochaete found in the Blood of a Wild Rat. *Proc. Soc. Exper. Biol. and Med.*, Vol. IV, p. 125.

MANSON-BAHR, P. (1921). Manson's Tropical Diseases. London, 7th Ed., p. 217.

MARTINOTTI, L. (1917). Contribuzione allo studio del Sodoku. *Giorn. Ital. d. Malattie Ven. e. d. Pelle.*, Vol. LVIII, No. 2, pp. 116-135.

MATSUSAKI, S., and TSUNEMOCHI, R. (1917). Rat-Bite Fever Treated with Imamicol. *Tokyo Iji Shinji*, No. 2049, p. 2335.

de MELLO, F., and MENEZES, C. F. (1917). Um caso de Sodoku em Goa. *Bol. Ger. Med. Farmacia.* Nova Goa, Vol. IV, No. 5, p. 175.

MENDELSON, R. W. (1919). Tropical Diseases Observed in Siam. *Jour. Amer. Assoc.*, Vol. XVII, p. 1199.

MESNIL, F. (1906). *Bull. de l'Ins. Pasteur*, Vol. IV., p. 992.

MEZINESCU, D. (1909). Sur un spirillose du rat (Note préliminaire). *Compte. rend. Soc. Biol.*, Vol. LXVI, p. 58.

de MICAS (1895). *Arch. Méd. de Toulouse*, Vol. I, p. 170.

MIDDLETON, G. S. (1910). Rat-Bite Fever. *Lancet*, Vol. I, p. 1618.

Millot-Carpentier (1884). *L'Union Méd.*, Vol. XXXVIII, p. 1069.

Miura, M., and Toriyama, N. (1897). *Ztschr. d. med. Gesellsch. z. Tokyo*, Vol. XI, p. 1059.

Miyake, H. (1900). *Mitt. a. d. Grenzgeb. d. Med. u. Chir.*, Vol. V, p. 231.

Mouchet and Guillermin (1923). Le premier cas de sodoku observé en Turquie. *Bull. et Mém. Soc. Méd. Hôpit. de Paris.* 3rd Ser., Vol. XXXIX, No. 5, p. 202.

Mühlens, P. (in Kolle, W. and Wasserman, G.) (1913). Handbuch der pathogenen Mikroorganismen. Jena, 2nd Edit., Vol. VII, p. 921.

Muller, O. R. P. (1918). A Case of Rat-Bite Fever in Sydney. *Med. Jour. of Australia*, Vol. i, No. 26, p. 531.

Nakano, H. (1917). Spirochaetes of Rats and Mice. *Hifukwa Hitsunyokwa Zasshi.* (Japan. *Zeitschr. f. Derm. u. Urol.*), Vol. XVII, No. 2, p. 1.

Nicolle, C., and Blanc, G. (1917). Premier enquête sur l'existence, chez le rat de Tunis, des spirochètes pathogènes pour le cobaye. *C. R. Soc. Biol.*, Vol. LXXX, No. 9, p. 445.

Nicholson, F. (1913). A Further Case of Rat-Bite Disease. *The Practitioner*, Vol. XCI, p. 429.

Niowaka, I., Yoshizawa, I., and Mumemoto, E. (1917). Spirochaetosis in the Guinea-Pig. *Tokyo Iji Shinshi*, No. 2007.

Nixon, J. A. (1922). The Infecting Agent in Rat-Bite Fever. (Correspondence) *Lancet*, Vol. ii, p. 1304.

Nixon, J. H. (1914). 'Rat-Bite Fever' caused by a Ferret. (Memoranda). *Brit. Med. Jour.*, Vol. ii, p. 629.

Oda, Z. (1915). Two Cases of Rat Bite treated by Salvarsan. *Sei.-i.-Kwai Med. Jour.*, Vol. XXXIV, p. 52.

Ogata (1909). *Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo*, Vol. VIII, p. 287.

——— (1911). *Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo*, Vol. IX, p. 343.

——— (1913-14). *Mitt. a. d. med. Fakult. d. k. Univ. z. Tokyo*, Vol. XI, p. 179.

Parmanand, M. J. (1923). Rat Bite Fever with Special Reference to its Aetiological Agent. (Preliminary Communication). *Indian Jour. Med. Res.*, Vol. XI, No. 1, p. 181.

Pellegrini, A. (1923). Il Sodoku in Italia. *Riforma Med.*, Vol. XXXIX, No. 16, p. 363.

Peña y Maya, F. (1885). *Siglo Med.*, Vol. XXXII, p. 117.

Perugia, A., and Carchidio, U. (1915). Le Malattie da Morso di Topo (Sodoku, Rattenbisskrankheit). *Riforma Medica*, Vol. XXX, No. 9, p. 229, and No. 10, p. 256.

Piazza, C. (1916). Un nuovo caso di Sodoku. *Morgagni.*, Vol. LVIII, p. 67.

Pondman, A. (1917). Een geval van Rattenbeetsiekte. *Geneesk. Tijdschr. v. Nederl.-Indië.*, Vol. LVII, No. 3, p. 368.

Powell, A., and Bana, F. D. (1918). Treatment of Rat-Bite Fever with Injections of Cacodylate of Soda. *Indian Med. Gaz.*, Vol. LIII, p. 376.

Proescher, F. (1911). *Internat. Clin.* Series 21, Vol. IV., p. 77.

——— (1912). *Berl. klin. Woch.*, Vol. XLIX, p. 841.

Ramond, F., and Levy-Bruhl (1917). Un Nouveau cas de Sodoku. *Bull. et Mém. Hôpit. de Paris.* 3. Sér., Vol. XXXIII, No. 29, p. 1086.

Reasoner, M. and Nichols, H. J. (1920). The Use of Arsphenamin in Non-syphilitic Diseases. *Jour. Amer. Med. Assoc.*, Vol. XLV, p. 645.

Reece, M. (1872). *Med. Exam.*, Vol. XIII, p. 51.

Reid, T., and Ritchie, J. (1915). A Case of Rat-Bite Fever. *Edinburgh Med. Jour.*, New Ser., Vol. XV, No. 3, p 186.

Remlinger, P. (1917). Un cas de Sodoku observé au Maroc. *Bull. Soc. Path. Exot.*, Vol. X, No. 2, p. 120.

Row, R. (1917). On a New Species of Spirochaete from a Case of Rat Bite Fever in Bombay. *Indian Jour. Med. Res.*, Vol. V, No. 2, p. 386.

——— (1917). Cutaneous Spirochaetosis produced by Rat Bite in Bombay. *Bull. Soc. Path. Exot.*, Vol. XI, No. 3, p. 188.

——— (1922). Some Cutaneous Manifestations in Rat Bite Spirochaetosis. *Trans. Roy. Soc. Trop. Med. and Hyg.*, Vol. XVI, No. 4, p. 203.

Sangiorgi, G. (1922). Le spirochetosi dei muridi (Considerazioni critiche), Nota 1. *Pathologica*, Vol. XIV, No. 323, p. 253.

——— (1922). Le spirochetosi dei muridi. Nota 2a (Proposta del sottogenere '*Treponemella*'). *Pathologica*, Vol. XIV, No. 329, p. 461.

Sano, T. (1917). Rat Bite Disease ? Case Report. *Iji Shimbun*, No. 981, p. 1153.

Schottmüller, H. (1914). *Derm. Woch.*, Vol. LVIII, Suppl. 77.

Shikami, (1909). *Zeit. med. Ges.*, Tokyo (Cited by Futaki).

de Sousa, L. (1917). Segunda caso de Sodoku em Goa. (Diagnostico retrospectivo). *Bol. Ger. Med. Farmacia.*, Nova Goa, Vol. IV., No. 5, p. 179.

Spaar, R. C. (1923). Two Cases of Rat-Bite Fever. Rapid Cure by the Intravenous Injection of Neo-salvarsan. *Jour. Trop. Med. and Hyg.*, Vol. XXVI, No. 14, p. 239.

Surveyor, N. F. (1913). A Case of Rat-Bite Fever treated with Neo-salvarsan. *Lancet.*, Vol., ii, p. 1764.

Tanoka, I. (1918). Cat-Bite Disease. *Juzenkai Zasshi.*, Vol. XXIII, No. 2, p. 5.

Thomson, J. G. (1923). The Common Occurrence of Pseudospirochaetes in the Blood of Blackwater Fever Cases and of Normal Human Beings, and Animals when using the Technique of Blanchard and Lefrou. *Jour. Trop. Med. and Hyg.*, Vol. XXVI, p. 251.

Tileston, W. (1916). Etiology of Rat Bite Fever. *Jour. of American Med. Assoc.*, Vol. LXVI, No. 14, p. 995.

Tsuneoka, R. (1917). Ueber die Spirochaeta von Rattenbisskrankheit. *Kyoto Igaku Zassi*, Vol. XIV, No. 4, p. 46.

Tunnicliff, R. (1916). Streptothrix in Broncho-pneumonia of Rats, similar to that of Rat-Bite Fever. (A Preliminary Report). *Jour. of American Med. Assoc.*, Vol. LXVI, No. 21, p. 1606.

——— (1916). Streptothrix in Broncho-pneumonia of Rats, similar to that in Rat-Bite Fever. *Jour. Infect. Dis.*, Vol. XIX, No. 6, p. 767.

Tunnicliff, R., and Mayer, K. R. (1918). A Case of Rat-Bite Fever. *Jour. Infect. Dis.*, Vol. XXIII, No. 6, p. 555.

Tyzzer, E. E. (1907). A Series of Spontaneous Tumours in Mice. *Soc. Exper. Biol. and Med.*, Vol., IV, p. 85.

Umemoto, E. (1920). The Effects of Platinum Chloride upon some Spirochaetes. *Tokyo Iji Shinshi*, No. 2189, p. 1479.

Walch, E. W. (1923). Twee gevallen van Rattebeetziekte. *Geneesk. Tijdschr. v. Nederl.-Indië.*, Vol. LXIII, No. 2, p. 239.

Wenyon, C. M. (1906). Spirochaetosis of Mice due to *Spirochaeta muris*, n. sp. in the Blood. *Jour. of Hyg.*, Vol. VI, No. 5.

Wilcox, W. (1840). *Amer. Jour. Med. Sci.*, Vol. XXVI, p. 245.

Wright, J. H. (1904). *Jour. Med. Research.*, Vol. XIII, p. 349.

Yamada, J. (1917). Rat-Bite Fever. Spontaneous Transmission from Giunea-Pigs to Rabbits. *Tokyo Iji Shinji*, No. 2054, p. 2577.

Yamada, K. (1917). Rat-Bite Fever due to the Scratch of a Cat. *Saikingaku Zasshi.*, No. 265, p. 877.

Zannini, W. (1914). Due Nuove Casi di Sodoku in Italia. *Gazz. d. Ospedali e. d. Cliniche.*, Vol. XXXV, No. 75, p. 793.